REMARKS

This response is due on July 29, 2004 by virtue of the attached petition and fee for a one-month extension of time to respond. Applicants respectfully request that the claims be reconsidered for allowance in view of the attached remarks.

I. Status of the Claims

Claims 1-40 are pending in the instant application, and stand variously rejected under 35 U.S.C. §102(b), 35 U.S.C. §103(a) and under 35 U.S.C. §112 first paragraph as allegedly lacking enablement, and under 35 U.S.C. §112 second paragraph. Applicants respectfully traverse the rejections and request reconsideration in light of the above amendments and the following remarks.

II. Rejection under 35 U.S.C. §102(b), should be withdrawn

Claims 1 and 2 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Kamada (Cellular and Molecular Neurobiology); claims 1, 2, 10, 11, 19 and 20 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Rasenick (J. Clin. Psychiatry); claims 1 and 2 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated Chen (J. Neurochem.) and claims 1, 2, 5, 7, 10, 11, 14, and 16 were rejected under 35 U.S.C. §102(b) over Young (J. Affective Disorders). Applicants respectfully traverse each of these rejections.

In order for a claim to be anticipated, a single item of prior art must disclose ***each*** element of the claim. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q.2d 81, 90 (Fed. Cir. 1986). Applicants have amended claim 1 and 10 to specifically clarify that the peripheral cells being referred to in the claims are blood cells. Neither Kamada, Rasenick nor Chen can serve as legitimate anticipatory references for these claims or any claims dependent therefrom as asserted by the Examiner, because these references do not disclose blood cells as model systems for determining the efficacy of an antidepressant therapy. Applicants request that each of the 35 U.S.C. §102(b) rejections based on Kamada,

Rasenick and Chen be withdrawn in view of the amendment to claims 1 and 10 that explicitly recite the cell type.

Claims 1, 2, 5, 7, 10, 11, 14, and 16 are novel over the disclosure of Young (J. Affective Disorders). Claims 1 and 10 have been amended to recite that the modification is a "redistribution of Gsα from a strongly hydrophobic region of the plasma membrane to a less hydrophobic membrane domain." This redistribution of the Gsα in the peripheral blood cells of individuals being tested for effectiveness of antidepressant therapy is not taught in Young. In the absence of such a disclosure, Young cannot anticipate the instant claims.

Applicants submit that neither Kamada, Rasenick, Chen nor Young anticipate the claims of the present invention and as such rejections under 35 U.S.C. §102(b) based on these references should be withdrawn.

III. Rejection under 35 U.S.C. §103(a), should be withdrawn

Claims 3, 4, 6, 8, 9, 12, 15, and 17-18 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Young. Claims 21, 22, 32, and 33 were rejected under 35 U.S.C. §103(a) as assertedly unpatentable over Rasenick (J. Clin. Psychiarty). Claims 23-31 and 34-40 were rejected under 35 U.S.C. §103(a) as being unpatentable over a combination of Rasenick in view of Young. Applicants respectfully traverse these rejections.

a. The rejection over Young alone should be withdrawn

As an initial matter, the disclosure of Young has been mischaracterized and a discussion of the Young disclosure, as well as the disclosure of the present invention, may clarify matters. Firstly, it is noted that the Examiner states that Young "teaches on page 202, antidepressants stimulate G protein to enhance the coupling with adenylyl cyclase." Applicants submit this statement is taken out of context. The text that Applicants believe the Examiner is referring to states:

". . .forskolin stimulates the catalytic activity of AC directly, as well as the activated complex between the catalytic unit of AC and the stimulatory G-protein subunit

(αs), especially at lower concentrations. . .Such effects suggest that antidepressant treatments may enhance coupling between αs and AC. ***However, not all investigators. . . concur with these findings. . . chronic AD [antidepressant drug] treatments do not produce consistent changes in α-subunit abundance"***

Thus, reviewing the statement identified by the Examiner in the context of the paragraph in which it is cited, Young, on its face, indicates that the skilled artisan does not believe that G-proteins have a role in monitoring the effects of antidepressant application. More importantly, the entirety of the remainder of the Young disclosure is focused on establishing that antidepressants ***do not produce an effect on MNL*** G-protein levels or function in depressed patients (see title), and that ***instead, the antidepressants are having an effect on adenylyl cyclase.*** Examining the disclosure of Young further, it becomes evident that Young examines membranes prepared from mononuclear leukocytes (MNL) from a small group of depressed patients treated for 5 weeks with (and either responding or not responding to) four different antidepressants. MNL from patients with major depressive disorders were assayed for adenylyl cyclase and, the disclosure shows that adenylyl cyclase was increased in those who responded to antidepressant treatment. However, it is an important distinction that Young was measuring ***adenylyl cyclase***, not ***extracting G protein with detergent***. Again, Young expressly indicates that there is no effect on G protein levels or function in MNLs as a result of antidepressant treatment (see for example discussion, where it is stated "the lack of differences in MNL αs and αi levels at baseline . . .suggesting that expression of these G-protein α subunits is not altered. . . " Young page 204, second column). This further refutes the statement at page 202 relied upon by the Examiner. Furthermore, Young measured basal adenylyl cyclase, a measurement that is independent of G protein activation. Thus, the Young disclosure suggests that the antidepressant effect being monitored in MNLs is related to adenylyl cyclase activity and is independent of G protein function because Young expressly states the G-protein levels or function are not affected by antidepressant treatment.

In contrast to the disclosure of Young, the present invention clearly demonstrates that there is an association of G-protein subunits with the components of the

plasma membrane or cytoskeleton components of blood cells. More specifically, the present invention shows that antidepressant treatment produces a shift in the cellular localization of G-protein alpha subunit and that shift in the G-protein alpha subunit localization is specific to Gsα. These findings, for the first time, allowed the inventors to determine whether a given antidepressant will be effective by assessing whether or not the antidepressant being tested produces a shift in the cellular localization of Gsα. There is no teaching or suggestion anywhere in Young of such a shift in Gsα localization.

With the above differences in the disclosure of Young and the present application in mind, Applicants submit that the Young disclosure cannot support an obviousness rejection of the claims. As is well-established in the case law, in order to render obvious a claimed invention, the cited art must disclose each element of the claimed invention. Here there is no teaching of the redistribution of the localization of Gsα in blood cells as a result of antidepressant treatment. The absence of such a teaching, combined with the fact that Young states that G-protein function and expression is not altered as a result of antidepressant treatment, means that there is no motivation from the teachings of Young to look to the localization of Gsα in MNLs. Indeed, given that Young suggests that it is basal adenylyl cyclase levels that are affected by antidepressant therapy and that there is no effect of G-proteins at all, one of skill in the art would not even be motivated to determine the localization of any G-protein subunit, let alone Gsα specifically, as taught by the present application and recited in the claims.

For the above reasons, the obviousness rejection based on Young should be withdrawn.

b. The rejection over Rasenick alone should be withdrawn

The Examiner cites Rasenick (J. Clin. Psychiatry) as allegedly rendering obvious claims 21, 22, 32 and 33. Applicants respectfully traverse.

Claims 21 and 22 are dependent from claim 19 and claims 32 and 33 are dependent from claim 31, with the exception of the dependencies claims 32 and 33 resemble the language of claims 21 and 22, which recite:

> 21. [original] The method of claim 19 wherein the modification is a redistribution of Gsα from a strongly hydrophobic region of the plasma membrane to a less hydrophobic membrane domain.
>
> 22. [original] The method of claim 19 where the modification is a redistribution of Gsα from cell processes and process tips to the cell body.

The Rasenick disclosure being cited by the Examiner at page 52 states simply that "chronic antidepressant treatment in rats increases coupling between Gsα and adenylyl cyclase." At page 54, there is another generic statement "that chronic exposure of C6 glioma cells to antidepressant or antibipolar drugs modifies adenylyl cylase ***by some*** intervention between Gsα and the enzyme." These are two general and generic statements. These statements say nothing about "redistribution of Gsα from a strongly hydrophobic region of the plasma membrane to a less hydrophobic membrane domain." These statements say nothing about antidepressants causing such a redistribution. These statements say nothing about the fact that the redistribution is specific to Gsα. These statements say nothing about the fact that such redistribution of Gsα can be used as an indicator of the efficacy of a given antidepressant. These statements merely are a generic recognition of the fact that there is "some intervention" or interaction between Gsα and adenylyl cyclase. This generic recognition cannot be used to render obvious claims that expressly recite a physical modification (i.e., redistribution) of a specific G-protein subunit (i.e., Gsα) in response to a specific stimulus (i.e., antidepressant treatment.) These specific parameters of claims 21, 22 and 32 and 33 cannot be ignored and in the absence of a teaching of these parameters, the rejection under 35 U.S.C. §103(a) over Rasenick must be withdrawn.

The Examiner's statement that it would have been "to redistribute G protein because such proteins when stimulated or inhibited by various agents would be expected to

be found in different distribution" (see office action page 6) is unsupported by any scientific evidence and appears to have been arrived at through hindsight reconstruction upon review of the instant application. Moreover, as specifically stated at page 54, first column, Rasenick taught that"

> "Since it was suggested that antidepressant exposure might alter the distribution of these G proteins or their ability to attach to the membrane, membrane and cytosolic fractions were probed individually. ***Again, there was no difference between controls and anti-depressant treated cells.***"

Thus, contrary to the Examiner's assertion it would seem that Rasenick, on its face, refutes that fact the distribution of G proteins is altered in cells response to antidepressant treatment. Furthermore, the other art cited by the Examiner (i.e., Young) quite clearly suggests that it is adenylyl cyclase and not G-protein subunits that are affected by the antidepressants and as such, at best the suggestion in the art is that it is adenylyl cyclases that are "stimulated or inhibited by" the antidepressants. In view of all of the above, Applicants respectfully submit that the Examiner's assertions cannot support an obviousness rejection of claims 21, 22, 32 and 33. Applicants respectfully request that the rejections of these claims cased on Rasenick be withdrawn.

c. The rejection over Rasenick in combination with Young should be withdrawn

The Examiner combines the teachings of Rasenick with the teachings of Young stating that Young, at page 202, teaches that antidepressants stimulate G-protein to enhance the coupling with adenylyl cyclase. As discussed in section (a) above, this is a "straw-man" argument in Young that Young sets up in the introduction of the paper and then immediately proceeds to introduce data that tear down the argument and conclude instead that there is a "lack of effect of antidepressants on mononuclear leukocyte G-protein levels or function in depressed outpatients" (see Title) and that "expression of these G-protein α subunits is not altered in MDD" (see page 204). Rasenick itself teaches that there is no effect on the distribution of the G-protein subunits between the membrane and cytosolic fractions

(see above). Thus, it would seem that the combined teaching show that there is no effect on G-protein activity, and there is no effect on distribution on G protein subunits as a result of antidepressant treatment. Therefore, the combined disclosure of Rasenick and Young teach the exact opposite of what the Examiner asserts. As such, Applicants submit that the claims of the invention cannot be rendered obvious by this opposite teaching.

IV. Rejection under 35 U.S.C. §112, first paragraph for lack of enablement should be withdrawn

Claims 1-40 were rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The following discussion shows that the claims are fully enabled by the specification as filed (section (b) below). This discussion is further corroborated by data provided in the attached declaration of Dr. Mark Rasenick (section (c) below).

a. The rejection

The rejection for lack of enablement is recited at page 7-8 of the application and states in its entirety that:

> "Claim 1 is directed to detecting the effectiveness of antidepressant therapy, and claim 19 is directed t assaying for an agent having antidepressant activity. The specification as originally filed teaches effects of various known antidepressants upon content of G protein and resultant adenylyl cyclase activity. Further, on page 20 Table 4 shows known antidepressants change G distribution in cells. On page 22, Example 13 is directed to screening for effectiveness of antidepressant therapy and for agents having antidepressant activity, however it is merely description with no screening having been performed, no data presented, and most importantly, no correlation between the putative mechanism of action and actual results are seen. No effectiveness of any agents nor screening for any unknown agents having been administered is found in the specification. The leap from a putative mechanism of action to real world application based upon a mechanism of action has not been made. No new antidepressant agents have been identified. Given the known difficulty in studying antidepressant activity, the specification is not enabling for doing so."

Applicants respectfully submit that the above paragraph not only fails to establish lack of enablement of the claims of the present invention, it points to certain of the sections in the specification that actually provide the enablement.

The issues raised by the Examiner in the above-recited paragraph are addressed in further detail below. Initially, however, Applicants submit that the legal principle for enablement is that the specification teach one of skill in the art ***whatever is now claimed.*** It is respectfully submitted that the claims of the present invention are not directed to a specific mechanism of action, although clearly there is one involved as an underlying principle for the invention, and nor are the claims directed to any " new antidepressant agents."

b. The rejection should be withdrawn because the *Wands* factors show that the claims to methods are fully enabled.

The claims of the invention, as exemplified by claim 1 and claim 19 presented herein above are directed to "determining the effectiveness of antidepressant therapy in a depressed individual comprising determining whether there has been a modification of the association of Gsα with components of the plasma membrane or cytoskeleton of cells from peripheral tissues wherein said peripheral tissues are blood cells of the depressed individual and wherein said modification is a redistribution of Gsα from a strongly hydrophobic region of the plasma membrane to a less hydrophobic membrane domain of blood cells of the depressed individual wherein such a modification indicates that said antidepressant therapy is effective." As the Examiner correctly points out, the "specification as originally filed ***teaches effects of various known antidepressants upon content of G protein*** and resultant adenylyl cyclase activity. Further, on page 20 Table 4 ***shows known antidepressants change G distribution*** in cells." It is evident that the specification has taught that antidepressants cause a redistribution of Gsα in the cells of a subject being treated with antidepressants. By determining whether or not such a redistribution occurs in blood cells of an individual upon treatment with a putative antidepressant agent one skilled in the art will be able to predict whether that agent will be effective as an antidepressant or not, i.e., if redistribution occurs,

the agent will serve as an antidepressant. Setting up such a screen requires merely a stepwise following of the teachings of the specification.

The Examiner admits that screening for effectiveness of antidepressant therapy and for agents having antidepressant activity is described but criticized the application because "no screening having been performed, no data presented, and most importantly, no correlation between the putative mechanism of action and actual results are seen." Applicants respectfully object to this criticism because it calls for a description of working examples. However, it is a long-established tenet that "a specification need not contain a working example if the invention is otherwise disclosed in a manner that one skilled in the art would be able to practice it without an undue amount of experimentation." *In re Borkowski,* 422 F2d 904 (CCPA 1970). The Examiner's statement that "no effectiveness of any agents nor screening for any unknown agents having been administered is found in the specification" misses the point that the invention is directed at new way of showing the efficacy of an antidepressant agent. Such a new way, *i.e.*, new method, can be shown with known antidepressant compositions and does not necessarily require identification of an unknown antidepressant. Similarly, the Examiner's argument that "no new antidepressant agents have been identified" also is inapplicable. The subject matter being claims is a method, not an antidepressant.

Applicants submit that the factors from *In re Wands* 858 F.2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988) for determining whether the specification provides enablement commensurate with the scope of the claims are fulfilled and that the claims of the present application are in full compliance with the edicts of *In re Wands*. Applying the standards summarized in *Wands*, the present specification does indeed provide a reasonable amount of guidance to one of skill in the art.

The methods of the present invention provide a teaching of how to use peripheral tissues such as blood cells to determine whether antidepressant therapy will be effective. The parameter used to monitor the efficacy is whether Gsα in the blood cells of the individual receiving such therapy undergoes redistribution in response to the application of

the antidepressant. As the Examiner admits, Table 4 on page 20 quite clearly demonstrates this is possible.

One skilled in the art could readily use other antidepressants in the same manner as shown in Table 4 to determine whether the requisite redistribution occurs. Performing such methods of the invention will require ***only some routine*** experimentation. As the court in *In re Wands* instructed "[e]nablement is not precluded by the necessity for some experimentation." Indeed, it is inevitable that there may be some quantity of experimentation required. Nonetheless, the key word is ***undue***, and not experimentation. *In re Wands*, 8 USPQ2d 1400, 1404. The court went on to state that a considerable amount of experimentation is, in fact, permissible if it is merely routine ***or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*** *Id.* Therefore, the first and second *Wands* criteria *i.e.*, (1) that the quantity of experimentation not be undue and (2) the presence of guidance/direction in the specification of how to perform the methods are met.

Moreover, while it is true that not all of the factors need to be addressed, other *Wands* factors argue in favor of enablement. For instance, the nature of the claimed invention is one in which the level of skill of the ordinary artisan is high. The field of the invention is in the area of screening for distribution of Gsα in the plasma membrane of cells to see whether the Gsα has from a strongly hydrophobic region of the plasma membrane to a less hydrophobic membrane domain of the membrane. Such determinations of membrane fractionation techniques are a matter of routine skill in the art. However, prior to the present invention, there was no recognition in the art that there was a specific redistribution of Gsα in response to antidepressant therapy. That recognition and guidance was presented for the first time by the inventors in the present specification. Thus, the state of the prior art (another *Wands* criterion) was that the skilled artisan could determine the localization of G-proteins within membrane fractions, but the redistribution of specific subunits of G proteins in response to antidepressant therapy was not known, appreciated or contemplated by the prior art.

Furthermore, the breadth of the claims is fully commensurate in scope with the teachings provided in the specification. The claims are directed to methods of determining the effectiveness of a therapy by assessing whether or not a physical redistribution of Gsα occurs. These methods are exactly what is exemplified in the specification. Therefore, the applicants have enabled the full scope of their claimed invention and, as the courts have indicated the '[i]nventor should be allowed to dominate . . . others . . . based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work." (*In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970).

The above discussion of some of the *Wands* factors as applied to the claims of the present application shows that the claimed methods of the present invention are adequately and objectively enabled, by the specification as filed. As such, the applicants respectfully request withdrawal of the rejection under §112, first paragraph, and reconsideration of the claims for allowance.

c. The rejection should be withdrawn because the attached declaration by Dr. Rasenick shows that the redistribution of Gsα occurs with antidepressants but not with agents that are not antidepressants.

In addition to the above discussion, attached hereto is a declaration from Dr. Rasenick in which Dr. Rasenick provides data to demonstrate that drugs that have a structure that is similar to a known antidepressants but are known not have antidepressant properties did not have an effect of Gsα redistribution whereas the antidepressant drugs exhibited the property of moving Gsα out of cytoskeleton-associated domains into a more detergent soluble fraction of the membrane.

In the attached declaration, a direct comparison is provided between the redistributive effects of fluoxetine as compared to the lack of effect of the fluoxetine analog LY368514 (see graph in Rasenick declaration paragraph 6). Fluoxetine is also known as Prozac™ (see Rasenick declaration paragraph 4), a well-known antidepressant. LY368514 has a structure that is almost identical to fluoxetine, but for the fact that the CF3 that is in a

para position in fluoxetine is in the ortho position in the LY368514 compound (see Rasenick declaration, paragraph 4). While fluoxetine has antidepressant activity, the structurally-related compound LY368514 does not act as an antidepressant (see Rasenick declaration, paragraph 4). The data shown in paragraph 6 of the Rasenick declaration, demonstrate that an antidepressant and a closely related compound that does not have antidepressant activity can be differentiated by their effects on Gsα redistribution. The agent that has antidepressant activity causes a causes a shift in the localization of Gsα from a TTX-100 insoluble lipid raft rich domain to a more TTX-100 soluble domain, whereas the closely structurally related compound that does not antidepressant activity, fails to have such an effect (see Rasenick declaration paragraphs 7 and 8).

In addition to fluoxetine, Dr. Rasenick also describes data obtained using desipramine (a tricyclic antidepressants) and structurally related compounds that are not antidepressants (tricyclic compounds similar in structure to desipramine e.g., chlorpromazine, an antipsychotic) or other uptake inhibiting drugs that are not antidepressants (amphetamine)(see Rasenick declaration paragraphs 6, 7 and 9). Desipramine had a similar effect to fluoxetine in causing a redistribution of Gsα (see Rasenick declaration paragraph 6 and 7) whereas the agents that are not antidepressants did not have such an effect (see Rasenick declaration paragraph 9).

The data provided in the Rasenick declaration clearly demonstrated that the screening assays of the present invention which are based upon determining whether the agent being tested produces a redistribution in the localization of Gsα can be used to distinguish whether will have antidepressant activity or not.

In view of the fact that the *Wands* determination as applied to the claims of the present application would show that the claimed methods of the present invention are adequately and objectively enabled, by the specification as filed and further in view of the additional data described in the Rasenick declaration, the Applicants respectfully request

withdrawal of the rejection under §112, first paragraph, and reconsideration of the claims for allowance.

V. Rejection under 35 U.S.C. §112, second paragraph should be withdrawn

Claims 1-18 and 30-40 were rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention.

More particularly, claim 1 was objected to for reciting that "detecting" effectiveness rather than "determining" effectiveness and the Examiner has further objected to the claim for not positively reciting a step to determine effectiveness, indicating that a "correlating step may be intended." (see page 8 of Office Action). Further, claim 30 was objected to for reciting the term "having the ability", which allegedly renders the claim indefinite because, as indicated by the examiner, compounds have an activity, not ability.

Claim 1 has been amended to replace the term "detecting" with the term "determining" and further to positively recite a correlative step. A similar amendment has been effected in Claim 10. Applicants believe this addresses the rejection.

Claim 30 has been amended to replace the term "the ability to modify" with the term "an activity that modifies." Applicants believe this amendment addresses the rejection of claim 30.

Applicants submit that the above amendments and comments address all of the rejections based on 35 U.S.C. §112, second paragraph and request that the rejections be withdrawn in light of these comments.

VI. Conclusions

Applicants believe that all of the rejections have been overcome and the claims of the instant application are now in condition for allowance and request an early

indication of such a favorable disposition of the case. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

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Respectfully submitted,

By _____

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